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EXAMINER	
BOESEN, AGNIESZKA	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/659,036	FITZGERALD ET AL.	
	Examiner	Art Unit	
	Agnieszka Boesen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 12-27* is/are pending in the application.

4a) Of the above claim(s) *19,25 and 26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 12-18, 20-24, and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Amendment filed March 19, 2007 in response to the Office Action of September 19, 2006 is acknowledged and has been entered. Claims 1 and 7 have been amended. Claims 8-11 were canceled. New claims 12-26 were added. Claims 19, 25 and 26 are withdrawn because the claims are drawn to a non-elected invention. Claims 1-7, 12-18, 20-24, and 27 are currently examined.

Election/Restriction

Newly submitted claims 19, 25, and 26 are directed to species that are independent or distinct from the species originally claimed for the following reasons:

This application contains claims directed to the following patentably distinct species: epitopes derived from HIV, herpes, vaccinia, cytomegalovirus, yersinia, vibrio, herpes zoster, influenza, hepatitis, tuberculosis, *Chlamydia, Salmonella, Trypanosoma, and Plasmodium* as well as other protozoan of claims 19, 25, and 26. The species are independent or distinct because the different organisms from which the epitopes are derived are distinct structurally and have distinct disease etiology.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Currently, claims 1-6 are generic.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Claims 19, 25, and 26 are drawn to epitopes comprised in the chimera used in the presently claimed method. The epitiope such as V3 loop apex of HIV-1 has been examined on the merits and thus the epitopes derived from herpes, vaccinia, cytomegalovirus, yersinia, vibrio, herpes zoster, influenza, hepatitis, tuberculosis, Chlamydia, Salmonella, Trypanosoma, and Plasmodioum as well as other protozoan of claims 19, 25, and 26 are withdrawn from examination because they are drawn to a non-elected species. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 112

Rejection of claims 1-7 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement **is withdrawn** in view of Applicants arguments and amendments to the claims.

Applicant's arguments have been fully considered. Applicant points out that the instant specification on page 27, describes a number of cell recognition domain polypeptides and on page 47 the specification provides a working example of epitope domains. Applicant amended the claims to narrow the length of the epitope domain. Applicant argues that because the guidance with regard to the cell recognition domains and epitopes can be readily found in the prior art (Applicant cites a number of references with regard to prior art teaching of cell recognition domains), those skilled in the art would have had all the required information to make and use the chimeric construct of the present invention. Applicant further argues that in

order to comply with the written description requirement, the specification need not describe what can be found in the prior art. Examine agrees with Applicant's arguments and thus the rejection is withdrawn.

Rejection of claims 1-7 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a PE-like chimeric particle that has the V3 loop substituted between the cysteines in the Ib region, does not reasonably provide enablement for a 1500 aa cell recognition domain and a 1500 aa foreign epitope domain while maintaining essential structures required for the functions of domains II and III, **is withdrawn** Applicants arguments and amendments to the claims.

New Rejections in view of Applicant's amendment.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 12-18, 20-24, and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a translocation domain comprising an amino acid sequence at least 90% identical to the sequence of *Pseudomonas* exotoxin A (PE) (SEQ ID NO: 2) from amino acid position 280 to amino acid position 344 thereof and wherein the domain effects translocation to the cytosol, does not reasonably provide enablement for a translocation domain comprising an amino acid sequence at least 90% identical to the sequence of *Pseudomonas* exotoxin A (PE) (SEQ ID NO: 2) from amino acid position 280 to amino acid position 344 thereof and wherein the domain *is capable* of effecting translocation to the cytosol.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are drawn to a method of eliciting a secretory IgA-mediated immune response in a subject comprising administering, to at least one mucosal surface, *Pseudomonas* exotoxin A-like chimeric immunogen comprising a translocation domain comprising an amino acid sequence at least 90% identical to the sequence of Pseudomonas exotoxin A (PE) (SEQ ID NO: 2) from amino acid position 280 to amino acid position 344 thereof and wherein the domain is capable of effecting translocation to the cytosol. The current specification discloses that:

> [0120] "The amino acid sequence sufficient to effect translocation can be derived from the translocation domain of native PE. This domain spans amino acids 253-364. The translocation domain can include the entire sequence of domain II. However, the entire sequence is not necessary for translocation. For example, the amino acid sequence can minimally contain, e.g., amino acids 280-344 of domain II of PE. Sequences outside this region, i.e., amino acids 253-279 and/or 345-364, can be eliminated from the domain. This domain also can be engineered with substitutions so long as translocation activity is retained."

Thus the specification provides that the translocation activity of the present chimera must be necessarily retained in order to enable one skilled in the art to practice the claimed method with a reasonable expectation of success. Therefore the activity and functionality of the translocation domain comprised within the chimera is pivotal for the purpose of the current invention. The present claims allow for 10% variability within the translocation domain. The specification discloses that the translocation domain can be engineered with substitutions so long as translocation activity is retained. However the current claims do not recite that the translocation activity must be retained. Thus for the reasons discussed above, the skilled artisan

would be unable to practice the present invention with a reasonable expectation of success and therefore the present invention is not enabled as claimed.

Claim Rejections - 35 USC § 103

Rejection of claims 1-7 under 35 U.S.C. 103(a) as being unpatentable over Cryz et al. (Vaccine, 1995) in view of Bukawa et al. (Nature Medicine, 1995) as evidenced by Cryz et al. (Infection and Immunity, 1986) **is withdrawn** in view of Applicant's amendment.

Applicant amended the claims to recite that the epitope domain of the present chimera is inserted into the Ib domain of PE, with or without deletion of native Ib amino acid sequences. Neither Cryz nor Bukawa teach *the amino acids sequence of the epitope is inserted into the Ib domain of PE, with or without deletion of native Ib amino acid sequence*. Thus the rejection is withdrawn.

However in view of Applicant's amendment and newly found prior art new rejections are made.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7, 12-15, 18, 20-24, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cryz et al. (Vaccine, 1995) as evidenced by Cryz et al. (Infection and Immunity, 1986) in view Pastan et al. (U.S. Patent 5,328,984) and Bukawa et al. (Nature Medicine, 1995).

The claimed invention is directed to a method of eliciting secretory IgA-mediated immune response to an epitope in a subject by administering a non-toxic Pseudomonas exotoxin-A chimeric immunogen. The non-toxic *Pseudomonas* exotoxin-A chimeric immunogen comprises: (1) a cell recognition domain (2) a translocation domain comprising an amino acid sequence at least 90% identical to the sequence of *Pseudomonas* exotoxin A (PE) (SEQ ID NO: 2) from amino acid position 280 to amino acid position 344 thereof and wherein the domain effects translocation to the cytosol (3) epitope domain comprising amino acid sequence between about 5 and about 350 amino acids wherein the amino acids sequence of the epitope is inserted into the Ib domain of PE, with or without deletion of native Ib amino acid sequences, wherein the epitope comprises a V3 loop apex of HIV-1, and (4) an ER retention domain.

The claims recite an open language with regard to a content of a translocation domain. The specification discloses that "a translocation domain comprising an amino acid sequence substantially identical to a sequence of PE domain II is sufficient to effect translocation to a cell cytosol" (see [0016]). Thus the limitation with regard to the translocation domain is anticipated by a sequence of PE domain II, because the amino acid sequence at least 90% identical to the sequence of *Pseudomonas* exotoxin A (PE) (SEQ ID NO: 2) from amino acid position 280 to amino acid position 344 thereof and wherein the domain is comprised within PE domain II.

Cryz (Vaccine, 1995) teaches a method of eliciting an immune response by administering *Pseudomonas* exotoxin A-like chimeric immunogen comprising a V3 loop apex of HIV-1 epitope, which is also called a principal neutralizing determinant PND (see the entire document, particularly page 67 and Materials and Methods). Cryz (Vaccine, 1995) teach HIV-1 peptide epitopes of 15-50, 5-15, and 15-350 amino acids in length (see Table 2). Cryz (Vaccine, 1995)

does not expressly teach that exotoxin A is derived from *Pseudomonas*, but refers to another reference by Cryz (Infection and Immunity, 1986) discussing purification of exotoxin A from *Pseudomonas*.

Cryz, 1995 does not teach chimeric immunogen wherein the amino acid sequence of the epitope is inserted into the Ib domain of PE, with or without deletion of native Ib amino acid sequences". However based on the teaching of Pastan et al. who teach a chimeric construct identical to the chimera of the present invention and who teach insertion of an epitope into the Ib domain of PE between two cysteines which form a cysteine-cysteine loop (see column 3, lines 21-38, and 65-69, column 11, lines 29-44, and column 12, lines 15-18 and 44-55), it would have been obvious to the skilled artisan to provide a chimera of the present invention. One would have been motivated to insert an epitope into the Ib domain of PE, because Pastan et al. teach that the goal of introducing specific peptides into cell cytoplasm using his chimeric construct can be accomplished by inserting peptides/epitopes into Ib domain of PE (see column 12, lines 44-55). One would have had a reasonable expectation of success to provide a chimera of the present invention wherein the epitope is introduced into Ib domain of PE because such construct has been successfully made as evidenced by Pastan et al.

Pastan et al., does not teach using his chimera to induce IgA-mediated immune response. Cryz (Vaccine, 1995) teach administration of the chimeric immunogen by intramuscular route and generation of IgG antibodies against the immunogen but Cryz does not teach administering Pseudomonas exotoxin A-like chimeric immunogen to mucosal surfaces. Bukawa teaches mucosal administration of a chimeric immunogen comprising cholera toxin and HIV-1 derived

foreign epitope. Administration of Bukawa's chimeric immunogen results in generation of IgA-mediated immune response (see the entire document).

It would have been obvious to the person of ordinary skill in the in the art to administer Pseudomonas exotoxin A-like chimeric immunogen comprising an epitope derived from V3 loop apex of HIV-1 to mucosal surfaces in order to elicit IgA-mediated immune response.
One would have been motivated to administer the immunogen taught by Cryz to mucosal surfaces as taught by Bukawa, because Bukawa teaches that control of pandemic infection of HIV-1 requires means of developing mucosal immunity against HIV-1 because sexual transmission of the virus occurs mainly through mucosal tissues.

One would have had a reasonable expectation of success of inducing IgA-mediated immune response by mucosal administration of the chimeric immunogen because Bukawa's chimeric immunogen comprising cholera toxin and HIV-1 derived epitope has been successfully used to elicit IgA-mediated immune response when administered by mucosal route.

Therefore the present invention would have been *prima facie* obvious to the person of ordinary skill in the art at the time when the invention was made.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cryz et al. (Vaccine, 1995) as evidenced by Cryz et al. (Infection and Imunity, 1986) in view Pastan et al. (U.S. Patent 5,328,984) and Bukawa et al. (Nature Medicine, 1995) as applied to claim 1 and further in view of Cardy et al. (WO95/31483 of record in IDS of 7/7/2006).

Claims are drawn a method of eliciting secretory IgA-mediated immune response to an epitope in a subject by administering a non-toxic *Pseudomonas* exotoxin-A chimeric

immunogen. Claim 16 is drawn to a specific cell recognition domain comprised within the chimera of the present invention, such as single chain Fv fragment.

None of the references discussed above teach cell recognition domain such as single chain Fv fragment. Cardy et al. teach a chimeric construct for delivery of antigens into cell cytosol wherein the cell recognition domain is a single chain Fv fragment of an antibody, Cardy et al. calls the cell recognition domain an "effective portion" (see page 3, page 6, page 10, and page 13).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to provide a chimeric construct intended for delivery of antigens to cell cytosol comprising a single chain Fv fragment as a cell recognition domain. One would have been motivated to provide the chimeric construct of Cryz (Vaccine, 1995) comprising Cardy's single chain Fv fragment of an antibody as a cell recognition domain. One would have a reasonable expectation of success to make such a construct because the recombinant DNA technology used for making such constructs has been well established in the art.

Therefore the present invention would have been *prima facie* obvious to the person of ordinary skill in the art at the time when the invention was made.

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cryz et al. (Vaccine, 1995) as evidenced by Cryz et al. (Infection and Imunity, 1986) in view Pastan et al. (U.S. Patent 5,328,984) and Bukawa et al. (Nature Medicine, 1995) as applied to claim 1 and further in view of Roberge et al. (Journal of Immunology, 1989, Vol. 143, p. 3498-3502).

Claims are drawn a method of eliciting secretory IgA-mediated immune response to an epitope in a subject by administering a non-toxic Pseudomonas exotoxin-A chimeric immunogen. Claims 17 is drawn to a specific molecule that should be recognized and bound by a cell recognition domain comprised within the chimera of the present invention, wherein the specific molecule is the IL-2 receptor.

None of the references discussed above teach cell recognition domain binding IL-2 receptor. Roberge et al. teach a *Pseudomonas* toxin chimeric construct comprising IL-2 binding to IL-2 receptor expressed on T cells (see the entire document).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to provide a chimeric construct intended for delivery of antigens to cell cytosol wherein cell recognition domain binds IL-2 receptor. One would have been motivated to provide the chimeric construct of Cryz (Vaccine, 1995) comprising Roberge's cell recognition domain bidning Il-2 receptor. One would have a reasonable expectation of success to make such a construct because the recombinant DNA technology used for making such constructs has been well established in the art.

Therefore the present invention would have been *prima facie* obvious to the person of ordinary skill in the art at the time when the invention was made.

Conclusion

Applicant's amendment necessitated the new ground of rejections presented in this Office action. Thus, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Agnieszka Boesen whose telephone number is 571-272-8035. The examiner can normally be reached on Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Agnieszka Boesen, Ph.D.

/Stacy B. Chen/ 6-5-2007
Primary Examiner, TC 1600